REMARKS

Claims 1-52 were pending prior to this Response, with claims 2, 3, 6, 7 and 33-52 having been withdrawn from further consideration pursuant to 37 C.F.R § 1.142(b). By the present communication, no claims have been added, claims 1, 9, 27, 28 and 32 have been amended, and claims 2, 3, 6, 7, 24, 25 and 33-52 have been canceled without prejudice. The amended claim language adds no new matter, being fully supported by the Specification and original claims. Specifically, support for the phrase "mammalian" in claims 1 and 32 may be found at page 21, lines 16-21. Support for the phrase "by determining the level of transcription from" in claim 9 may be found at page 20, lines 11-13. Accordingly, claims 1, 4, 5, 8-23 and 26-32 are currently pending in this application.

Information Disclosure Statement

The Information Disclosure Statement (IDS) has been objected to as allegedly being improper by not listing all patents, publications or other information submitted for consideration by the Office. Specifically, one of the references cited in the IDS appears to have a typographical error. Attached herewith is a corrected IDS Form 1449 listing the correct spelling of Sommers, et al. for consideration by the Office.

Objection to the Specification

The specification has been objected to because of a typographical error on page 22, first paragraph. Applicants have amended the paragraph to replace the phrase "tern yeast" with "term yeast" as suggested by the Examiner. Furthermore, Applicants have canceled claims 2, 3, 6, 7 and 33-52 without prejudice due to their encompassing non-elected subject matter. Accordingly, reconsideration and withdrawal of the objections to the specification are respectfully requested.

Rejection of under 35 U.S.C. §112

Applicants respectfully traverse the rejection of claims 9-18 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claim 9 (including claims 10-18 dependent therefrom) is allegedly vague and indefinite for the recitation "measured indirectly". Applicants have amended claim 9 to define the invention with greater particularity. Accordingly, reconsideration and withdrawal of the rejection of claims 9-18 are respectfully requested.

Rejection of under 35 U.S.C. §102

Applicants respectfully traverse the rejection of claims 1, 4, 5, 8-25, 27 and 29-32 under 35 U.S.C. § 102(a) as allegedly being anticipated by Sommers et al. (IDS, Biochemistry 39:6898-6909, 2000; hereinafter "Sommers"). Applicants respectfully submit that the invention method for identifying constitutively activating mutations in a receptor or an ion channel, as defined by amended claim 1, distinguish over the disclosure of Sommers by requiring providing a library of coding sequences for potentially activating mutations of a candidate receptor or ion channel, which library is generated by replacing coding sequences for small or medium side-chain amino acids with coding sequences for large side-chain amino acids, wherein said small or medium side-chain amino acids are located in or proximate transmembrane segment(s) of the receptor or ion channel; expressing said library in mammalian host cells; measuring the activity of the encoded receptor or ion channels in said mammalian host cells; and identifying those coding sequence(s) which encoded activated receptors or ion channels.

Sommers allegedly discloses a method for identifying constitutively activating mutations by making a library carrying random as well as site directed mutations in the amino terminus and transmembrane regions of the STE2 gene in yeast. Sommers screened libraries of random mutations for constitutive alleles to determine the frequency and diversity of mutations that cause activation of one particular G protein receptor, the yeast α-factor receptor. There is no discussion with regard to use of mammalian host cells in the assays of Sommers. Accordingly, Applicants respectfully submit

that Sommers does not teach use of mammalian host cells for expressing a library of coding sequences for potentially activating mutations and measuring the activity of the encoded receptor in the mammalian host cells.

Anticipation under 35 U.S.C. § 102(a) requires that the reference recite each and every element of the claims in a single document. Since Sommers et al. fails to disclose each and every element of the invention methods, as defined by amended claim 1, Applicant respectfully submits that the Examiner has failed to establish anticipation under 35 U.S.C. § 102(a) over Sommers et al. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of under 35 U.S.C. §103

A. Applicants respectfully traverse the rejection of claims 1, 4, 5, 8, 10, 19-24, 26 and 29-32 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Herrick-Davis et al. (hereinafter "Herrick-Davis") in view of Dahiyat et al. (hereinafter "Dahiyat"). The burden of proof in establishing a *prima facie* case of obviousness under § 103 clearly rests with the Patent Office. *In re Piasecki,* 745 F.2d 1468, 1472 (Fed. Cir. 1984). In establishing a *prima facie* case, the Patent Office, among other things, must show that (1) the prior art would have suggested to those of ordinary skill in the art that they should make the claimed invention and (2) that the prior art would have revealed a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). "Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure." *Id.* Thus, "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000). Further, when relying on the knowledge of persons of ordinary skill in the art, the Patent Office must "explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). "The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent has been reinforced in

myriad decisions, and cannot be dispensed with." *In re Sang Su Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002) (citations omitted).

To date, the Patent Office has failed to provide objective evidence of any suggestion or motivation in the prior art to combine and modify the particular references cited by the Office. Instead, the Office has simply recited elements gleaned from the various references and stated that the combination of these elements would have been obvious to one skilled in the art. It is well settled that the Patent and Trademark Office cannot pick and choose among the individual elements of assorted prior art references to recreate the claimed invention. *SmithKline Diagnostics, Inc. v. Helena Laboratories Corp.*, 859 F.2d 878, 887 (Fed. Cir. 1988). In addition, it is now well established that "[b]road conclusory statements regarding the teaching of multiple references standing alone are not 'evidence'." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999); see also *In re Kotzab*, 217 F.3d at 1370. "Th[e] factual question of motivation is material to patentability, and [can] not be resolved on subjective belief and unknown authority." *In re Sang Su Lee* 277 F.3d at 1343-44. Without such objective evidence to combine the references, it is inferred that the references were selected with the assistance of hindsight. *In re Rouffet*, 149 F.3d at 1358. It is well-established that the use of hindsight in the selection of references that comprise a case of obviousness is forbidden. *Id.*

The Examiner relies upon Herrick-Davis for disclosure of site directed mutagenesis to substitute amino acids with longer side chains or of different polarity with aromatic substitutions. Specifically, Herrick-Davis discloses that mutation of amino acid 312 from serine to phenylalanine or lysine in the serotonin 5-HT_2c receptor activates the receptor. However, Herrick-Davis does "not teach providing a library of coding sequences for potentially activating mutations of the candidate receptor protein and do not teach measuring the receptor activation with an indicator gene, which is modified by manipulation or replacement of the promoter sequence at the natural locus of the indicator gene and which is regulated by the receptor or ion channel in the host cell by using a heterologous reporter gene." (Office Action, page 8).

The disclosure of Dahiyat does not cure the above-described deficiencies in Herrick-Davis for teaching or suggesting the claimed invention. Dahiyat allegedly discloses a method of designing a protein library for the substitution of residues in any part of a protein, and that a protein sequence

can be designed through a fully automated sequence selection process to accomplish a library of a protein having various changes in the amino acids. While Dahiyat discloses that the automated sequence selection is an unbiased way of selecting amino acids for protein structure and function, and that it is not limited to a particular motif or folding sequences, Dahiyat does not teach or suggest expression of the library in mammalian host cells and measuring the activity of the encoded receptor in the mammalian host cells to identify those coding sequence(s) which encoded activated receptors. In fact, there is no discussion regarding screening mutants for activation of any receptors. Accordingly, there is no teaching or suggestion in Dahiyat to modify the invention of Herrick-Davis to arrive at a method for identifying constitutively activating mutations in a receptor by providing a library of potentially activating mutations and expressing the library in mammalian host cells.

B. Applicants respectfully traverse the rejection of claims 9, 11-18, 25 and 27 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Herrick-Davis in view of Dahiyat as applied to claims 1, 4, 5, 8, 10, 19-24, 26 and 29-32 and further in view of King et al. (hereinafter "King"). Applicants respectfully submit that the remarks above with regard to the differences between Herrick-Davis in view of Dahiyat and the invention as defined by amended claims 1 and 16 apply equally here. The Examiner relies upon King for disclosing that reconstruction of a heterologous reporter system using the β-galactosidase gene (lacZ) in yeast would elucidate understanding of a ligand binding to the G protein coupled receptor and its activation. However, King does not disclose expression of a library of mutant alleles in mammalian host cells to determine activation of a receptor by the mutants. Accordingly, there is no teaching or suggestion in King to modify the disclosure of Herrick-Davis in view of Dahiyat to arrive at a method for identifying constitutively activating mutations in a receptor by providing a library of potentially activating mutations and expressing the library in mammalian host cells.

C. Applicants respectfully traverse the rejection of claim 28 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Herrick-Davis in view of Dahiyat and King as applied to claims 1, 4, 5, 8-27 and 29-32 and further in view of Lerner et al. (U.S. Patent No. 6,051,386; hereinafter "Lerner"). Applicants respectfully submit that the remarks above with regard to the differences

between Herrick-Davis in view of Dahiyat and King and the invention as defined by amended claims 1 and 16 apply equally here. The Examiner relies upon Lerner for disclosing a method of identifying antagonists or agonists for G-protein coupled receptors using a pigment cell. However, Lerner is concerned with identifying new drugs through expression in pigment cells. There is no discussion regarding use of pigment cells to express a library of coding sequences for potentially activating mutations of a candidate receptor. Accordingly, there is no teaching or suggestion in Lerner to modify the disclosure of Herrick-Davis in view of Dahiyat and King to arrive at a method for identifying constitutively activating mutations in a receptor by providing a library of potentially activating mutations and expressing the library in mammalian host cells.

Applicant respectfully submits that *prima facie* obviousness of the invention over Herrick-Davis, Dahiyat, King and Lerner, either alone or in combination, has not been shown by the Examiner. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 for alleged lack of patentability are respectfully requested.

In summary, for the reasons set forth herein, Applicants maintain that claims 1, 4, 5, 8-23 and 26-32 clearly and patentably define the invention and respectfully request that the Examiner withdraw all rejections and pass the application to allowance. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

No fee is deemed necessary in connection of the filing of this document. However, the Commissioner is hereby authorized to charge for any additional required fees, or credit any overpayments to Deposit Account No. 07-1896.

Respectfully submitted,

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